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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/767,561	01/28/2004	Gordon J. Freeman	WYS-01804	5098

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EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/767,561	FREEMAN ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment, filed 08/07/2007, has been entered.

Claims 1-4 have been amended.

Claims 1-14 are pending.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Office Action.

This Action will be in response to applicant's arguments, filed 08/07/2007.

The rejections of record can be found in the previous Office Action, mailed 02/07/2007.

3. The filing date of the instant claims is deemed to be the filing date of priority application USSN 08/101,624, filed 7/26/03.

4. Upon reconsideration of applicant's amended claims and arguments, filed 08/07/2007, the previous rejection under 35 U.S.C. § 112, second paragraph, has been withdrawn.

5. The incorporation of essential material in the specification by reference to an unpublished U.S. application, foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference, if the material is relied upon to overcome any objection, rejection, or other requirement imposed by the Office. The amendment must be accompanied by a statement executed by the applicant, or a practitioner representing the applicant, stating that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter. 37 CFR 1.57(f).

Applicant's amendment claims 1-3, filed 08/07/2007, which now recite:
"a) at least 20 contiguous amino acids of SEQ ID NO: 2 or 4; or
b) a polypeptide that is at least 50% homologous to SEQ ID NO: 2 or 4".

However, these newly submitted "limitations: appear to rely upon the incorporation by reference to USSN 09/109,393 (see Appendix A: Excerpts of USSN 08/109,393) and not to the instant specification as filed.

With respect to Complete Disclosure Filed as set forth in MPEP 608.01(p); the following is noted.

If an application is filed with a complete disclosure, essential material may be canceled by amendment and may be substituted by reference to a U.S. patent or **>a U.S. patent application publication.< The amendment must be accompanied by **>a statement< signed by the applicant, or a practitioner representing the applicant, stating that the material canceled from the application is the same material that has been incorporated by reference >and no new matter has been included (see 37 CFR **1.57**(f). The same procedure is available for nonessential material.

If an application as filed incorporates * material by reference **>, a copy of the incorporated by reference material may be required to be submitted to the Office even if the material is properly incorporated by reference. The examiner may require a copy of the incorporated material to review and to understand what is being incorporated or to put the description of the material in its proper context. Another instance where a copy of the incorporated material may be required is where the material is being inserted by amendment into the body of the application to replace an improper incorporation by reference statement so that the Office can determine that the material being added by amendment in lieu of the incorporation is the same material as was attempted to be incorporated. If the Office requires the applicant to supply a copy of the material incorporated by reference, the material must be accompanied by a statement that the copy supplied consists of the same material incorporated by reference in the referencing application. See 37 CFR **1.57**(e).<

Therefore, for completeness of the instant specification, applicant is required to amend the instant specification to provide proper antecedent support for the newly added "limitations" indicated above.

Applicant is reminded that if the Office requires the applicant to supply a copy of the material incorporated by reference, the material must be accompanied by a statement that the copy supplied consists of the same material incorporated by reference in the referencing application. See MPEP 608.01(p) above.

6. This is a 35 U.S.C § 112, first paragraph, "written description" (and not new matter).

Claims 1-3 and 6-14 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed.

Applicant's amendment claims 1-3, filed 08/07/2007, now recite:
"a) at least 20 contiguous amino acids of SEQ ID NO: 2 or 4; or
b) a polypeptide that is at least 50% homologous to SEQ ID NO: 2 or 4".

There is insufficient written description of the genus set forth in instant claims 1-3 and dependent claims thereof, which now recite:

a) at least 20 contiguous amino acids of SEQ ID NO: 2 or 4; or

b) a polypeptide that is at least 50% homologous to SEQ ID NO: 2 or 4".

in the context of "nucleic acid molecules encoding B7-2 molecules and fragments thereof, which have the ability to costimulate a T cell and the ability to bind a CD28 or CTLA4", broadly encompassed by the claimed invention.

Applicant's arguments, filed 08/07/2007, have been fully considered but have not been found convincing essentially for the reasons of record.

With regard to the amended claims indicated above, applicant relies pages 11-12 of the instant specification; pages 4 and 14-15 of USSN 08/190,393; and Example 7 of U.S. Patent No. 6,130,316 for support for nucleic acid molecules encoding fragments of B7-2. In addition, applicant relies upon page 3 and 13 of USSN 08/109,393 and SEQ ID NOS. 2 and 4 for the support of the percent claimed percent homology and notes that SEQ ID NOS 2 and 4 are themselves 50% homologous with each other.

In contrast to the references cited in support of the rejection of record,

Applicant asserts that applicant was in possession of the relevant identifying characteristics such as the structure of other physical and/or chemical characteristics of the claimed genus of B7-2 molecules and fragments thereof in compliance with the Written Description guidelines.

With respect to applicant's reliance upon various screening assays,

the Court has held that the disclosure of screening assays and general classes of compounds was not adequate to describe compounds having the desired activity: without disclosure of which peptides, polynucleotides, or small organic molecules have the desired characteristic, the claims failed to meet the description requirement of § 112. See University of Rochester v. G.D. Searle & Co., Inc., 69 USPQ2d 1886,1895 (Fed. Cir. 2004).

The problem here is that the instant specification fails to provide a disclosure of which residues are required for the B7-2 molecule and fragments thereof that would retain the ability to costimulate a T cell and the ability to bind a CD28 or CTLA4

in B7-2 molecules and fragments thereof, other than the those B7-2 molecules isolated and cloned from a murine B cell tumor line M12 or from human anti-IgM activated B cells.

A skilled artisan cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus that exhibit this functional property.

Therefore, there is insufficient written description for genus of "B7-2 molecules comprising a limited sequence of nucleic acids encoding 20 amino acids or having 50% homology" to essentially two (2) examples of functional B7-2 molecules isolated and cloned from a murine and human cells, broadly encompassed by the claimed invention at the time the invention was made and as disclosed in the specification as filed under the written description provision of 35 USC 112, first paragraph.

The following of record is reiterated for applicant's convenience.

There is insufficient written description of the claimed genus of "B7-2 molecules" or "B7-2 molecules having the ability to costimulate a T cell and the ability to bind a CD28 or CTLA4" wherein the nucleic acids encode

a) at least 20 contiguous amino acids of SEQ ID NO: 2 or 4; or

b) a polypeptide that is at least 50% homologous to SEQ ID NO: 2 or 4".

in the absence of defining the relevant identifying characteristics such as the structure of other physical and/or chemical characteristics of the claimed genus and, in turn, there is insufficient written description of such identifying characteristics of the claimed genus of "B7-2 molecules and fragments thereof having the ability to costimulate a T cell and the ability to bind a CD28 or CTLA4" in the specification as-filed, commensurate in scope with the claimed invention.

For example, there is insufficient structural information or defining characteristics, which provide for a sufficient written description of the "B7-2 molecules and fragments thereof", as broadly claimed.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991). makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence. Thus, the specification fails to describe these DNA sequences. The Court further elaborated that generic statements are not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. Finally, the Court indicated that while applicants are not

required to disclose every species encompassed within a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, defined by nucleotide sequence, falling within the scope of the genus. See The Regents of the University of California v. Eli Lilly and Company, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

For example, the instant specification discloses specific species of murine and human B7-2 molecules and does not provide a sufficient number of species that support the claimed genus of "B7-2 molecules and fragments thereof having the ability to costimulate a T cell and the ability to bind a CD28 or CTLA4".

Applicant is relying upon certain biological activities and the disclosure of a limited number of species to support entire genera. Yet, the instant specification does not provide sufficient written description as to the structural features of said "B7-2 molecules and fragments thereof", as currently encompassed by the instant claims.

Also, the specification does not provide for a sufficient correlation between the chemical structure and the function of the genus of "B7-2 molecules and fragments thereof", currently encompassed by the claimed invention. The reliance on the disclosed limited examples of specific human and murine B7-2 molecules that meet the claimed "B7-2 molecules and fragments thereof" indicated above and disclosed in the specification as filed does not support the written description of any "B7-2 molecules and fragments thereof" broadly encompassed by the instant claims. It has been well known that minor structural differences even among structurally related compounds or compositions can result in substantially different biology, expression and activities. The specification as filed does not provide written description for "B7-2 molecules and fragments thereof", commensurate in scope with the claimed invention.

There is insufficient written description to lead a person of skill in the art to know which sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences for identifying "B7-2 molecules and fragments thereof having the ability to costimulate a T cell and the ability to bind a CD28 or CTLA4".

A person of skill in the art was not in possession of the breadth of claimed "B7-2 molecules and fragments thereof" because it was well known in the art at the time the invention was made that different molecules having sequence similarity to costimulatory molecules such as B7-1 and B7-2 have different, and often opposite, functions (e.g. reviewed by Riley et al., 2005, Blood, 105: 13 - 21; see entire document).

Also, Coyle et al. (Nature Immunology 2: 203-209, 2001) disclose that B7-1 and B7-2 exhibit pronounced differences in structural and functional characteristics (page 204, column 1; The B7-1 and B7-2 Family) and disclose the increasing complexity in costimulatory signal regulating T cell function, wherein a number of molecules are poorly understood and likely have distinct roles in regulation T cells (see entire document).

Further, even single amino acid differences can result in drastically altered functions between two costimulatory proteins. For example, Metzler et al. (Nature Structural Biol. 1997; 4:527-531) show that any of a variety of single amino acid changes can alter or abolish the ability of CTLA4 to interact with its ligands CD80 and CD86 (e.g., summarized in Table 2). Thus, one would not expect possession of the scope of the claimed genera by relying on functional activities that will be shared by two polypeptides having less than 100% identity over the full length of their sequences.

Attwood (Science 290: 471-473, 2000) teaches that "[i]t is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences.

Similarly, Skolnick et al. (Trends in Biotech. 18: 34-39, 2000) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2).

Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required

The instant claims do not provide sufficient structural and functional characteristics coupled with a known or disclosed correlation between function and structure. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus of "B7-2 molecules and fragments thereof".

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement makes clear that if a claimed genus does not show actual reduction to practice for a representative number of species; then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol.

66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3).

In the absence of structural characteristics that are shared by members of the genus of "B7-2 molecules and fragments thereof having the ability to costimulate a T cell and the ability to bind a CD28 or CTLA4",
the skilled artisan would conclude that the disclosure fails to provide a representative number of species to describe the genus.

Thus, Applicant was not in possession of the claimed genus. See University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Also, see MPEP 2163.

"Adequate written description requires a precise definition, such as by structure, formula, chemical name or physical properties, not a mere wish or plan for obtaining the claimed chemical invention." Id. at 1566, 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). Also see Enzo-Biochem v. Gen-Probe 01-1230 (CAFC 2002).

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Applicant is invited to limit the invention to the disclosed human and mouse "B7-2 molecules" to obviate this rejection.

9. Claims 1-3 and 6-14 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for certain nucleic acids encoding certain murine and human B7-2 encoding nucleic acids encoding the first peptide set forth in the claimed B7-2 fusion protein encoding nucleic acid and while being enabling for reliance upon known immunoglobulin constant regions for nucleic acids encoding the second peptide set forth in the claimed B7-2 fusion protein molecules as disclosed in the specification as filed, does not reasonably provide enablement for any

"B7-2 molecule and fragments thereof having the ability to costimulate a T cell and the ability to bind a CD28 or CTLA4"

"wherein the nucleic acid molecule encodes

a) at least 20 contiguous amino acids of SEQ ID NO: 2 or 4; or

b) a polypeptide that is at least 50% homologous to SEQ ID NO: 2 or 4".

The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's arguments, filed 08/07/2007, have been fully considered but have not been found convincing essentially for the reasons of record.

With regard to the amended claims indicated above, applicant relies pages 11-12 of the instant specification; pages 4 and 14-15 of USSN 08/190,393; and Example 7 of U.S. Patent No. 6,130,316 for support for nucleic acid molecules encoding fragments of B7-2. In addition, applicant relies upon page 3 and 13 of USSN 08/109,393 and SEQ ID NOS. 2 and 4 for the support of the percent claimed percent homology and notes that SEQ ID NOS 2 and 4 are themselves 50% homologous with each other.

In contrast to the references cited in support of the rejection of record,

applicant asserts that ample guidance as to how one skilled in art would make and use the claimed invention, including guidance for ex vivo modification of tumor cells and the type of tumor cells that may be modified with respect to the claimed genus of B7-2 molecules and fragments thereof in compliance with the enablement requirement of 35 USC 112, first paragraph.

In contrast to applicant's assertions, the instant specification does not provide sufficient guidance that would steer the skilled artisan towards those "B7-2 molecules and fragments thereof, particularly as to those nucleic acid / amino sequences with limited sequence or sequence homology responsible for retaining the ability to costimulate a T cell and the ability to bind a CD28 or CTLA4" that could be used to carry out the claimed methods – an essentially element of the every claim of the instant application – and has not provided sufficient evidence that such modifications were within the knowledge of the skilled or ordinary artisan at the time the invention was made.

Therefore, the amount of direction or guidance presented and the number of working examples provided in the specification as filed was narrowly limited to the known B7-2 molecules isolated and cloned from a murine B cell tumor line M12 or from human anti-IgM activated B cells.

What is missing from the specification as filed is the disclosure of sufficient direction or examples of how to modify tumor cells with nucleic acids encoding B7-2 molecules and fragments thereof relying upon limited sequences or sequence homology, other than the known murine and human B7-2 molecules.

The screening assays provide a starting point from which one of skill in the art can perform studies with the known B7-2 molecules to practice the claimed invention, but this is not adequate to constitute enablement in that will enable any person skilled in the art to make and use the invention as it reads on ill-defined modifications to these previously isolated and functional B7-2 molecules,

wherein the costimulatory molecules including the B7 antigens such as B7-2 exhibit pronounced differences in structural and functional characteristics.

See Coyle et al., Nature Immunology 2: 203-209, 2001; Metzler et al., Nature Structural Biol. 4:527-531, 1997; and Riley et al., Blood, 105: 13 – 21, 2005 cited of record and reiterated herein in the rejection under 35 USC 112, first paragraph, enablement.

One skilled in the art would not know the identity of any non-disclosed modifications to the known B7-2 molecules falling within the scope of the claim and consequently would not be able to make said non-disclosed B7-2 molecules and fragments thereof and use said non-disclosed B7-2 molecules and fragments thereof in the modification of tumor cells, broadly encompassed by the claimed invention.

Assays for investigating a known products is not equivalent for making and using ill-defined modifications.

If the skilled artisan cannot make the product, then the skilled artisan cannot use the product.

There is insufficient nexus to the specification and the claimed methods, which rely upon a genus of B7-2 molecules and fragments thereof.

In contrast to applicant's assertions, the instant specification does not provide sufficient guidance that would steer the skilled artisan towards modifications to B7-2 molecules and fragments thereof which the B7-2 molecules and fragments thereof would retaining the ability to costimulate a T cell and the ability to bind a CD28 or CTLA4 that could be used to carry out the claimed methods

Therefore, the amount of direction or guidance presented and the number of working examples provided in the specification as filed was narrowly limited to the known murine and human B7-2 isolated from B cells or B tumor cells.

"A recurring problem is whether a specification that sets forth a single or a limited number of examples can be enabling of broad claims when the subject matter concerns biological materials or reactions which are generally considered to be unpredictable."
See Enzo Biochem Inc. v. Calgene Inc. 52 USPQ2d 1129, 1138 (CAFC 1999).

Given the relative incomplete understanding in the biotechnological field involved, and the lack of a reasonable correlation between the narrow disclosure in the specification and the broad scope of protection sought in the claims, a rejection under 35 USC 112, first paragraph for lack of enablement is deemed appropriate.
See MPEP 2164.08.

A patent is granted for a completed invention, not the general suggestion of an idea and how that idea might be developed into the claimed invention. In the decision of Genentech, Inc. v. Novo Nordisk, 42 USPQ 2d 100,(CAFC 1997), the Court held that:
"[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" and that "[t]ossing out the mere germ of an idea does not constitute enabling disclosure". The court further stated that "when there is no disclosure of any specific starting material or of any of the conditions under which a process is to be carried out, undue experimentation is required; there is a failure to meet the enablement requirements that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art", "[I]t is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".

In contrast to appellant's assertions, the instant specification does not provide sufficient direction on how to make and use B7-2 molecules and fragments thereof as currently recited other than the isolated and functional B7-2 molecules relied upon the disclosure of the instant application as filed.

Without sufficient guidance, making and using "B7-2 molecules and fragments thereof which rely upon limited sequences or percent homology", other than limiting the "B7-2 molecules and fragments thereof to the known functional murine and human B7-2 molecules as disclosed and as defined in the specification as filed, would have been unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

The following is reiterated for applicant's convenience.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

The specification does not describe nor enable any "B7-2 molecule or fragment thereof having the ability to costimulate a T cell and the ability to bind a CD28 or CTLA4", as broadly encompassed by the claimed invention.

A person of skill in the art was not enabled to make and use the breadth of claimed "B7-2 molecule and fragment thereof" because it was well known in the art at the time the invention was made that different molecules having sequence similarity to costimulatory molecules such as B7-1 and B7-2 have different, and often opposite, functions (e.g. reviewed by Riley et al., 2005, Blood, 105: 13 - 21; see entire document).

Also, Coyle et al. (Nature Immunology 2: 203-209, 2001) disclose that B7-1 and B7-2 exhibit pronounced differences in structural and functional characteristics (page 204, column 1; The B7-1 and B7-2 Family) and disclose the increasing complexity in costimulatory signal regulating T cell function, wherein a number of molecules are poorly understood and likely have distinct roles in regulation T cells (see entire document).

Further, even single amino acid differences can result in drastically altered functions between two costimulatory proteins. For example, Metzler et al. (Nature Structural Biol. 1997; 4:527-531) show that any of a variety of single amino acid changes can alter or abolish the ability of CTLA4 to interact with its ligands CD80 and CD86 (e.g., summarized in Table 2). Thus, one would not expect the ordinary artisan to make and use the scope of the claimed genera by relying on functional activities that will be shared by two polypeptides having less than 100% identity over the full length of their sequences.

Attwood (Science 290: 471-473, 2000) teaches that "[i]t is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences.

Similarly, Skolnick et al. (Trends in Biotech. 18: 34-39, 2000) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2).

The instant claims do not provide sufficient structural and functional characteristics coupled with a known or disclosed correlation between function and structure. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus of "B7-2 molecules and fragments thereofhaving the ability to costimulate a T cell and the ability to bind a CD28 or CTLA4",

the skilled artisan would not have sufficient guidance and direction as to how to make and use the claimed "B7-2 molecules and fragments" as broadly claimed. For example, it has been well known that minor structural differences even among structurally related compounds or compositions can result in substantially different biology, expression and activities.

Further, applicant is relying upon certain biological activities and the disclosure of specific murine and human species of "B7-2 molecules" to support the genus of the claimed "B7-2 molecules and fragments thereof". Yet the instant specification does not provide sufficient guidance and direction how to make and use the scope of "B7-2 molecules and fragments thereof" by relying on limited sequences or homologous sequences, as encompassed by the claims.

Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality (e.g. B7-2 biological activity) requires a knowledge of and guidance with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which a polypeptide's structure relates to its functional usefulness. However, the problem of predicting polypeptide structure from mere sequence data of a limited number of amino acid and encoding nucleic acid sequences and, in turn, utilizing predicted structural determinations to ascertain binding or functional aspects of ligands and receptors (e.g., "B7-2 molecules") and finally what changes can be tolerated with respect thereto is complex and well outside the realm of routine experimentation. In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

Because of the lack of sufficient guidance and predictability in determining which structures would lead to "B7-2 molecules and fragments thereof having the ability to costimulate a T cell and the ability to bind a CD28 or CTLA4", other than those disclosed in the specification as-filed with the desired properties and that the relationship between the sequence of a nucleic acid encoding a functional costimulatory molecule structure as the relationship between structure-function was not well understood and was not predictable. It would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of "B7-2 molecules and fragments thereof", as broadly encompassed by the claimed invention.

In the absence of sufficient guidance and direction to the structural and functional analysis, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue to make and use "B7-2 molecules and fragments thereof having the ability to costimulate a T cell and the ability to bind a CD28 or CTLA4" based upon limited sequences and homologous sequences, other than relying on those murine and human "B7-2 molecules", as disclosed in the specification as-filed.

"It is not sufficient to define the recombinant molecule by its principal biological activity, e.g. having protein A activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992).

A patent is granted for a completed invention, not the general suggestion of an idea and how that idea might be developed into the claimed invention. In the decision of Genentech, Inc, v. Novo Nordisk, 42 USPQ 2d 100,(CAFC 1997), the court held that:

> "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" and that "[t]ossing out the mere germ of an idea does not constitute enabling disclosure". The court further stated that "when there is no disclosure of any specific starting material or of any of the conditions under which a process is to be carried out, undue experimentation is required; there is a failure to meet the enablement requirements that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art", "[I]t is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".

Without sufficient guidance, making and using "B7-2 molecules and fragments thereof having the ability to costimulate a T cell and the ability to bind a CD28 or CTLA4" other than limiting the disclosed murine and human "B7-2 molecules" in the specification as-filed as would have been unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Applicant is invited to limit the invention to the disclosed human and mouse "B7-2 molecules" to obviate this rejection.

10. Claims 1-14 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-25 of U.S. Patent No. 6,723,705.

Although the claims are not exactly the same, the recitation of "ex vivo" in the instant claims is encompassed by the patented claims and was either anticipated, immediately envisaged or an obvious variant of expressing B7-2 in tumor cells by direct injection of a nucleic acid encoding B7-2 into a tumor cell in order to increase the immunogenicity of tumor cells at the time the invention was made to one of ordinary skill.

Applicant's amendment, filed 08/07/2007, indicated that filing a terminal disclaimer will be considered when allowable subject matter is indicated.

11. No claim is allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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